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Copper-Mediated Oxidative Decarboxylative Coupling Reactions: Trifluoromethylation of Heteroarene C-H bonds with Trifluoroacetic Acid as the CF_3 Source and C-H Arylation of Benzoxazoles with Benzoic Acids

Lin Ju

Thesis submitted

to the C. Eugene Bennett Department of Chemistry

at West Virginia University

in partial fulfillment of the requirements for the degree of

Master of Science in

Chemistry

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Morgantown, West Virginia

2015

ABSTRACT

Copper-Mediated Oxidative Decarboxylative Coupling Reactions:
Trifluoromethylation of Heteroarene C-H bonds with Trifluoroacetic Acid as the CF_3 Source and C-H Arylation of Benzoxazoles with Benzoic Acids

Lin Ju

Compared with the prefunctionalized substrates in traditional cross-coupling reactions, carboxylic acid derivatives are easier to handle and commercially available in a broad scope, making them ideal starting materials to build biaryl structures. Copper has been demonstrated to decarboxylate carboxylic acids. There are also several examples of copper-mediated oxidative coupling reactions with two nucleophilic components. However, the copper-mediated direct C-H trifluoromethylation and arylation of heteroarenes with trifluoroacetic acid and benzoic acids is still challenging.

This thesis is divided into three chapters. Chapter I and Chapter II will describe copper-mediated oxidative decarboxylative trifluoromethylation of C-H bonds, including heteroarenes and arenes bearing a directing group, with trifluoroacetic acid as the trifluoromethylating reagent. Chapter III will focus on the catalytic synthesis of biaryl structures by copper-catalyzed decarboxylative cross-coupling with benzoic acids and benzoxazoles.

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Chapter I.

Copper-Mediated Oxidative Decarboxylative C-H Trifluoromethylation of Heteroarenes with Trifluoroacetic Acid as the CF_3 Source

1.1. Introduction

The trifluoromethyl group is a strong electron-withdrawing group. When incorporated into organic molecules, it can change their properties, like acidity, polarity and stability, which makes the organic structures bearing trifluoromethyl groups important in pharmaceuticals and agrochemicals.[1] Celebrex is a pain killer for the treatment of arthritis, Leflunomide can be used as an antirheumatic drug, Prozac is used for the treatment of depressive disorders and Januvia is an antidiabetic drug (Figure 1).[1] Each of these pharmaceuticals contains the trifluoromethyl group as an essential part for their biological activities. Because of the importance of the CF_3 group, the development of efficient trifluoromethylation methods has attracted considerable attention in recent years.[2] Various catalytic reactions for installing a CF_3 group have been developed using transition metals, including Pd,[15a, 15b] Ru,[2] Cu,[4-10] and others.[3] Compared with the transition metals mentioned above, copper is less expensive and can be more easily removed from the final product. Because of this, copper catalysts have been more extensively employed for introducing trifluoromethyl groups to arenes and heteroarenes.[4-10]

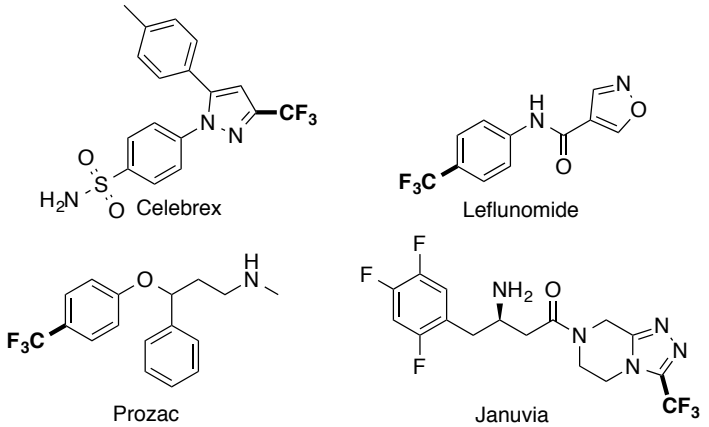
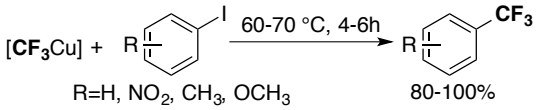


Figure 1. Examples of Pharmaceuticals and Agrochemicals Bearing CF_3 Groups

1.1.1. The Development of Trifluoromethyl Copper Complexes

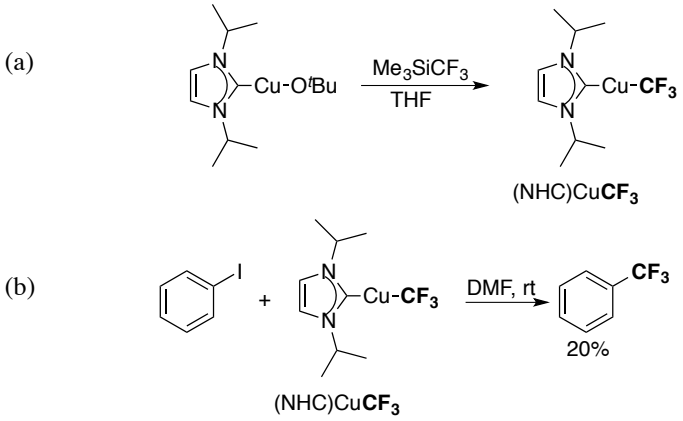
In 1986, Burton's group found that a trifluoromethyl copper complex reacts with iodobenzene to form the trifluoromethylated benzene. This result demonstrated that a trifluoromethyl copper complex can be directly utilized for the preparation of useful quantities of trifluoromethylated products (Eq 1).[4]



(1)

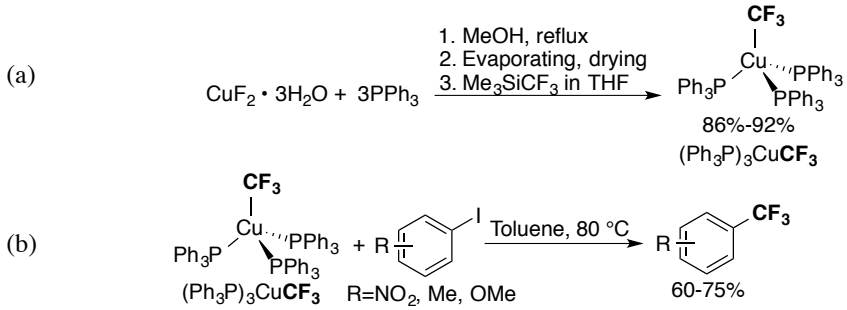
As time goes on, chemists have developed several kinds of trifluoromethyl copper complexes to build organic molecules containing trifluoromethyl groups. Below, three typical examples of trifluoromethyl copper complexes and the corresponding trifluoromethylation reactions will be discussed.

In 2008, Vicic's group reported the treatment of (NHC)Cu(O^{t}Bu) (NHC=N-Heterocyclic Carbene ligands) with Ruppert's reagent ($TMSCF_3$) to give rise to the NHC-stabilized (NHC)$CuCF_3$ (Scheme 1).[5] They further demonstrated that (NHC)$CuCF_3$ can react with iodobenzene to generate the corresponding trifluoromethylated benzene in 20% yield (Scheme 1).[5]

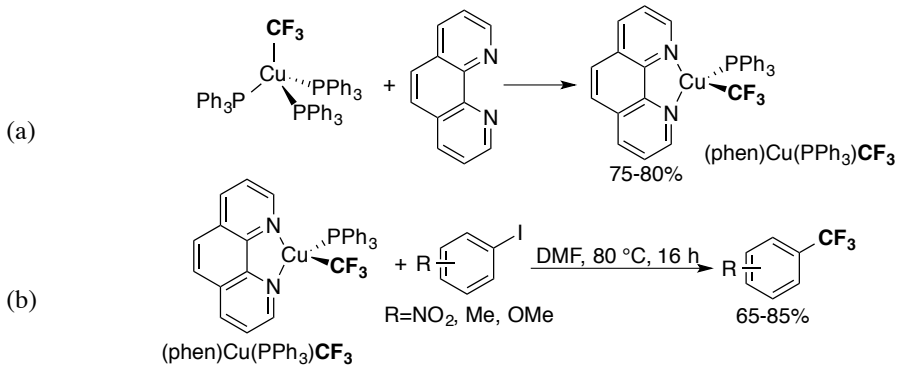


Scheme 1. Synthesis of (NHC)$CuCF_3$ and the Corresponding Trifluoromethylation of Iodobenzene

In 2011, Grushin's group developed the first procedure for the synthesis of $(PPh_3)_3CuCF_3$ (Scheme 2).[6] $(PPh_3)_3CuCF_3$ can trifluoromethylate haloarenes (Scheme 2). In addition, it can form (phen)Cu$(PPh_3)CF_3$ when reacting with 1,10-phenanthroline (Scheme 3).[6] Interestingly, (phen)Cu$(PPh_3)CF_3$ showed high reactivity in the trifluoromethylation of aryl iodides (Scheme 3).[6]

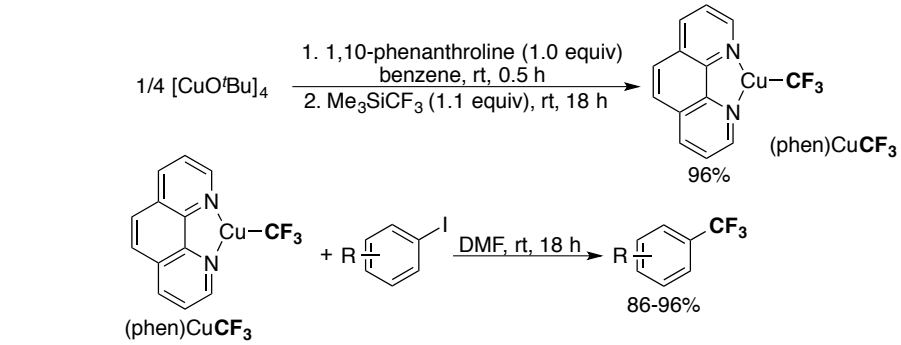


Scheme 2. Synthesis of $(PPh_3)_3CuCF_3$ and the Corresponding Trifluoromethylation of Iodobenzene



Scheme 3. Synthesis of (phen)Cu$(PPh_3)CF_3$ and the Corresponding Trifluoromethylation of Iodobenzene

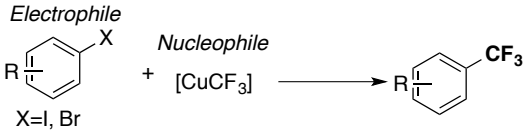
In 2011, Hartwig's group reported that $(CuO^tBu)_4$ reacts with 1,10-phenanthroline and $TMSCF_3$ to generate (phen)$CuCF_3$ (Scheme 4).[7] Furthermore, (phen)$CuCF_3$ reacts with iodoarenes to generate the corresponding trifluoromethylated arenes (Scheme 4).[7]



Scheme 4. Synthesis of (phen)$CuCF_3$ and the Corresponding Trifluoromethylation of Iodobenzene

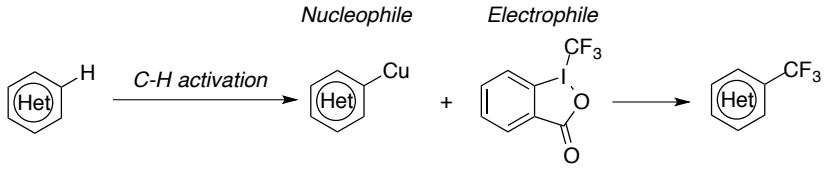
1.1.2. Copper-Mediated Oxidative Trifluoromethylation of C-H Bonds

There are various literature examples of copper-mediated trifluoromethylation of C-X bonds (X=I, Br).[4-7] A general idea of this kind of reaction is shown in Scheme 5. A nucleophilic trifluoromethyl copper complex reacts with electrophilic haloarenes (eg. aryl iodides and aryl bromides) to generate the trifluoromethylated coupling product, aryl-CF_3. However, these reactions require prefunctionalized iodoarenes or bromoarenes.



Scheme 5. Copper-Mediated Trifluoromethylation of Haloarenes

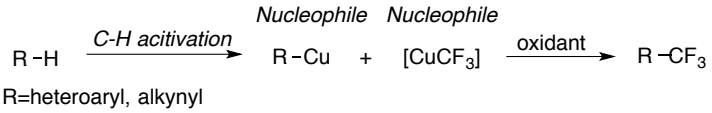
One other way to access trifluoromethylated heteroarenes is to use electrophilic trifluoromethylating reagents as shown in Scheme 6 to trifluoromethylate C-H bonds. Sodeoka's group reported a copper catalyzed trifluoromethylation of indole derivatives with Togni's reagent in 2010.[8] In this example, a nucleophilic heteroaryl generated from a copper-catalyzed C-H bond activation attacks the electrophilic CF_3^+ to form the carbon-carbon bond (Scheme 6). The drawback to this method is that the electrophilic trifluoromethylating reagents are very expensive compared with many other trifluoromethylating reagents (Figure 2).



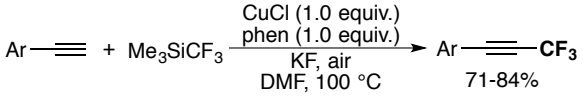
Scheme 6. Copper-Catalyzed C-H Trifluoromethylation of Heteroarenes with Electrophilic CF_3 Reagent

A more attractive way to introduce the CF_3 group onto (hetero)arenes is the direct trifluoromethylation of C-H bonds with a cheaper trifluoromethylation reagent. In 2010, Qing's group proposed an idea of "oxidative trifluoromethyaltion of C-H bonds".[9] This novel idea, shown in Scheme 7, indicated that the nucleophilic trifluoromethyl copper

complex could react with nucleophiles generated by activation of acidic C-H bonds to form trifluoromethylated coupling products in the presence of an oxidant. From this hypothesis, an efficient copper-mediated trifluoromethylation reaction of terminal alkynes (nucleophiles) with nucleophilic trifluoromethylating reagent ($TMSCF_3$) was successfully developed (Eq 2).

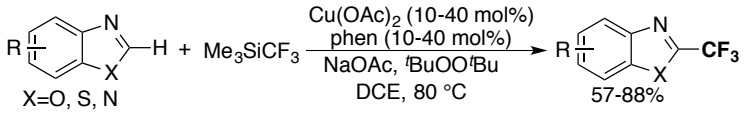


Scheme 7. Copper-Mediated Oxidative C-H Trifluoromethylation of Nucleophilic CF_3 Reagent



(2)

Two years later, a method for the copper-catalyzed oxidative trifluoromethylation of heteroarene C-H bonds with $TMSCF_3$ was published by the same group (Eq 3).[10] A wide range of aromatics, including benzoxazoles, indoles, benzothiazoles and benzoimidazoles, were converted into the corresponding trifluoromethylated derivatives in moderate to excellent yields (57%-88%).



(3)

1.1.3. Trifluoroacetic Acid as the CF_3 Source

In general, there are three classes of trifluoromethylating reagents as shown in Figure 2: (a) nucleophilic, (b) electrophilic, and (c) radical trifluoromethylating reagents. Even though the availability of these reagents has enabled the trifluoromethylation of various organic molecules, drawbacks still remain. Based on the prices shown in Figure 2, we can see that many of these molecules are very expensive. Many of these reagents also

generate large quantities of chemical waste when used. It is highly meaningful to identify trifluoromethylating reagents without these drawbacks and to develop efficient methods to trifluoromethylate organic molecules.

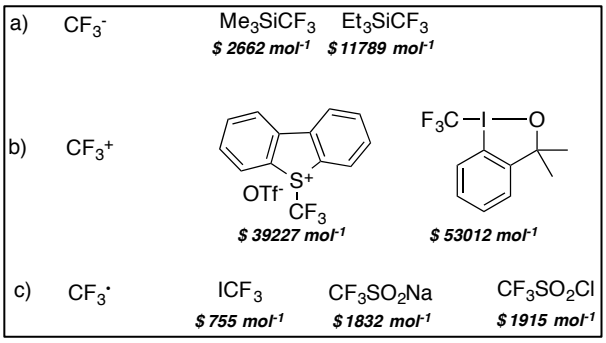


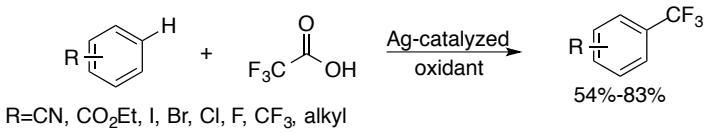
Figure 2. Prices of Some Common Trifluoromethylating Reagents

Compared with the trifluoromethylating reagents in Figure 2, trifluoroacetic acid (TFA) has several advantages. It is only $32 per mole, which makes it much cheaper than the reagents shown in Figure 2. In addition, CO_2 is the only byproduct generated from TFA after decarboxylation. More importantly, it would be highly desirable to expand trifluoromethylation to the haloalkylation with other haloalkyl carboxylic acids (RCO_2H, $R=(CX_2)_nCX_3$, X=F or Cl). A variety of haloalkyl carboxylic acids are commercially available while analogous haloalkylating reagents to those in Figure 2 are not.

Motivated by above advantages of TFA, it is highly desirable to develop a synthetic method for the decarboxylative trifluoromethylation reaction with TFA as the CF_3 source.

1.1.4. Oxidative Decarboxylative C-H Trifluoromethylation of Arenes with TFA as the CF_3 Reagent

Recently, Zhang's group published a silver-catalyzed oxidative C–H trifluoromethylation reaction of arenes using TFA as the trifluoromethylating reagent (Eq 4).[11] They successfully decarboxylated TFA and installed the trifluoromethyl group onto several substituted benzenes.



(4)

While this report broke through a new area of oxidative decarboxylative trifluoromethylation with TFA, the reaction can't trifluoromethylate heteroarenes (like pyridine) and shows low selectivity in the trifluoromethylation of substituted benzenes. It is highly desirable to find additional methods to selectively trifluormethylate arenes and heteroarenes.

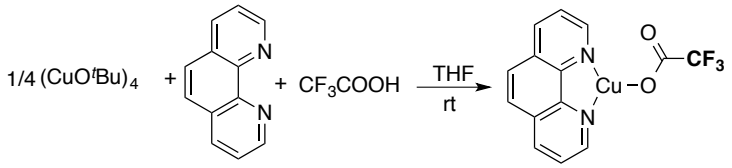
1.1.5. Project Objective

Scheme 8. Copper-Mediated Oxidative Decarboxylative C-H Trifluoromethylation of Heteroarenes with Trifluoroacetic Acid as the CF_3 Source

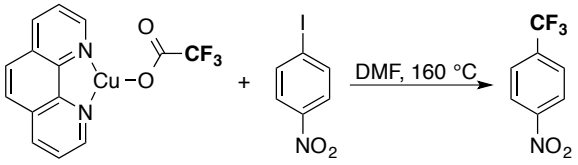
As described above, Vicic's group[12] and Buchwald's group[13] reported that copper can decarboxylate trifluoroacetate to trifluoromethylate aryl halides. Our goal is to develop a copper-mediated oxidative decarboxylative C-H trifluoromethylation of heteroarenes with trifluoroacetic acid as the trifluoromethylating reagent (Scheme 8).

1.2. Results and Discussion

Previous work in our group showed that the (phen)Cu(O_2CCF_3) complex can be synthesized by $(CuO^tBu)_4$ reacting with 1,10-phenanthroline and CF_3CO_2H at room temperature (Eq 5). Interestingly, treatment of this complex with *p*-nitro iodobenzene in DMF at 160 °C results in the fluorine signal of trifluoromethyl benzene by ^{19}F-NMR spectroscopy, which demonstrates that (phen)Cu(O_2CCF_3) can decarboxylate trifluoroacetate and install the trifluoromethyl group onto aryl iodides (Eq 6).

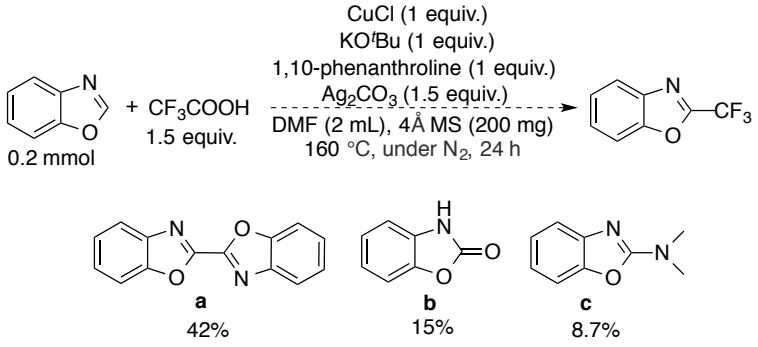


(5)



(6)

Based on this previous work, I replaced *p*-nitro iodobenzene with benzoxazole and applied this method to my new reaction (Scheme 9). Using a stoichiometric loading of CuCl, KO^{t}Bu and 1,10-phenanthroline (ligand), Ag_2CO_3 (1.5 equiv.) as the oxidant, 2 mL DMF as the solvent, at 160 °C, we found that benzoxazole reacted with CF_3COOH. We aimed to get the desired trifluoromethylated benzoxazole. But after purification, the desired product of trifluoromethyl benzoxazole was not observed. The benzoxazole dimer (**a**), benzoxazolone (**b**) and (dimethylamino)benzoxazole (**c**) were identified as the only products and these products have been published in the literature.[16]



Scheme 9. Reaction of Benzoxazoles and Trifluoroacetic Acid

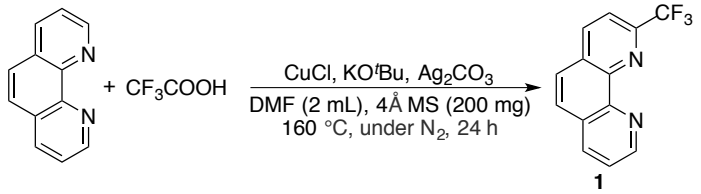
The ^{19}F-NMR spectrum of the crude reaction mixture showed a signal at -66.5 ppm, which is consistent with the signal of trifluoromethylated aromatics (-50 ppm to -70 ppm) according to the literature.[5-13] Furthermore, the result of GC-MS showed a mass-to-charge ratio of m/z = 248, consistent with the addition of a trifluoromethyl group to the phenanthroline ligand $[phenCF_3]^+$. Is it possible that the signal of -66.5 ppm from

trifluoromethyl phenanthroline? Being the curious type, I further set up an identical reaction but without benzoxazole (Table 1, entry 1). After purification, the 2-trifluoromethyl phenanthroline (**1**) was obtained with an isolated yield of 2% and further confirmed by comparison of the ^{1}H-NMR and GC-MS data to the literature.[14] This result demonstrated that our reaction conditions enable decarboxylation of TFA to trifluoromethylate 1,10-phenanthroline.

1.2.1. Control Reactions

A series of control reactions were done in order to know more about the reaction (Table 1). Without CuCl or phenanthroline, no reaction occurred, confirming copper is needed and phenanthroline is the source of product (entries 2 and 3). Higher loadings of CF_3CO_2H and KO^{t}Bu didn't increase the yield (entries 4 and 5). On the contrary, 2 equiv. of the oxidant (Ag_2CO_3) increased the yield to 4% (entry 6).

Table 1. Control Reactions of Trifluoromethylation of Phenanthroline[a]



1

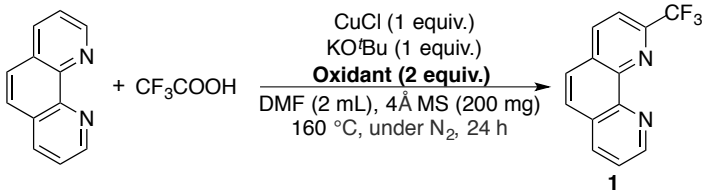
Entry	**phen**	CF_3CO_2H	CuCl	KO^{t}Bu	Ag_2CO_3	Yield (%)[b]
1	0.2 mmol	1.5	1	1	1.5	2.1[c]
2	0.2 mmol	1.5	–	1	1.5	NR
3	–	1.5	1	1	1.5	NR
4	0.2 mmol	3.0	1	1	1.5	2
5	0.2 mmol	1.5	1	2.5	1.5	2
6	**0.2 mmol**	**1.5**	**1**	**1**	**2**	**4**

[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), CuCl, KO^{t}Bu, Ag_2CO_3, CF_3CO_2H, and 4Å MS (200 mg) in DMF (2 mL) at 160 °C for 24 h under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard. [c]Isolated yield.

1.2.2. Oxidants Screening

Several types of oxidants were screened. For silver salts, (Table 2, entries 1-4), AgO_2CCF_3 increased the yield to 7% (entry 3). Other inorganic oxidants led to a reduction in reaction efficiency (entries 5 and 6). No **1** is observed when peroxides (entries 7 and 8) or benzoquinone (entry 9) are used as the oxidants. To our surprise, the same yield (7 %) of **1** was obtained both with and without KO^{t}Bu (entry 11). However, without CuCl, no **1** is formed (entry 12), which highlights the essential role of copper in this transformation. Running the reaction in the dark, covered with aluminum foil, didn't improve the yield (entry 13). Using a catalytic loading of CuCl lowered the yield to 4% (entry 14).

Table 2. Oxidants Screen and Corresponding Control Reactions[a]



1

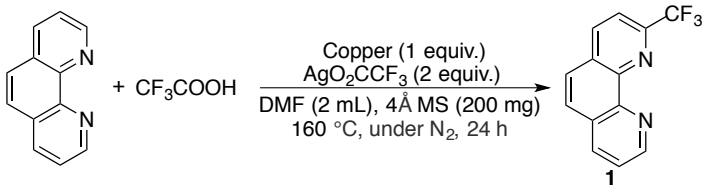
Entry	CuCl	KO^{t}Bu	Oxidants	Yield (%)[b]
1	1	1	Ag_2CO_3	4
2	1	1	Ag_2O	NR
3	**1**	**1**	**AgO_2CCF_3**	**7**
4	1	1	AgOTf	<2
5	1	1	$K_2S_2O_8$	<2
6	1	1	I_2	<2
7	1	1	^{t}BuOO^{t}Bu	NR
8	1	1	tBuOOH	NR
9	1	1	BQ	NR
10	1	1	--	<2
11	**1**	**_**	**AgO_2CCF_3**	**7**
12	_	1	AgO_2CCF_3	NR
13	1	–	AgO_2CCF_3	7[c]
14	20%	–	AgO_2CCF_3	4

[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), CuCl (1 equiv.), KO^{t}Bu (1 equiv.), oxidant (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) in DMF (2 mL) at 160 °C for 24 h under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard. [c]This reaction was done in the dark, covered with aluminum foil.

1.2.3. Copper Screening

With AgO_2CCF_3 identified as the best oxidant, Cu(I) and Cu(II) catalysts were explored as shown in Table 3. Cu(I) and Cu(II) halides gave similar yields (entries 1-3, 7 and 8). Using Cu_2O and CuO, lower yields were achieved (entries 5 and 9). Neither copper triflate nor copper acetate improved the yields (entries 4, 6, 11 and 12). Among all the copper salts tested, $Cu(O_2CCF_3)_2 \cdot xH_2O$ gave the highest yield (10%) of **1** (entry 10).

Table 3. Screening Table of Copper for Trifluoromethylation of Phenanthroline[a]



Entry	Copper	Yield (%)[b]
1	CuCl	6
2	CuBr	8
3	CuI	7
4	CuOAc	6
5	Cu_2O	3
6	$Cu(OTf)(CHCN)_4$	8
7	$CuCl_2$	7
8	$CuBr_2$	8
9	CuO	<2
10	**$Cu(O_2CCF_3)_2 \cdot xH_2O$**	**10**
11	$Cu(OTf)_2$	7
12	$Cu(OAc)_2 \cdot H_2O$	5

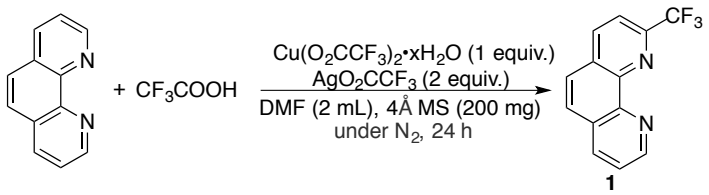
[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), copper (1 equiv.), AgO_2CCF_3 (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) in DMF (2 mL) at 160 °C for 24 h under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

1.2.4. Temperature Screening

The decarboxylation step is usually considered to require high temperatures.[12, 13] In 2013, Buchwald's group showed that higher temperatures (200 °C) improve

decarboxylation compared with a lower temperature (160 °C).[13] Unfortunatley, higher temperatures didn't improve our reaction (Table 4, entries 4-6). Even at 200 °C, the yield of **1** didn't change (entry 6). At lower temperatures, yields were lower, indicating decarboxylation wasn't efficient at temperatures lower than 160 °C (entries 1 and 2).

Table 4. Temperature Screening for Trifluoromethylation of Phenanthroline[a]



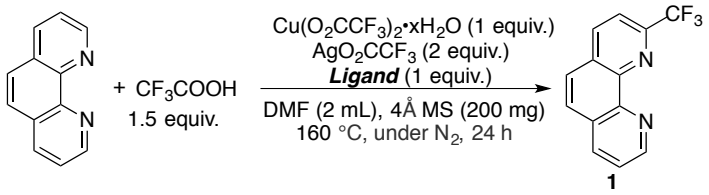
Entry	Temperature	Yield (%)[b]
1	110	NR
2	140	7
3	**160**	**10**
4	170	10
5	180	10
6	200	10

[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), $Cu(O_2CCF_3)_2•xH_2O$ (1 equiv.), AgO_2CCF_3 (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) in DMF (2 mL) for 24 h under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

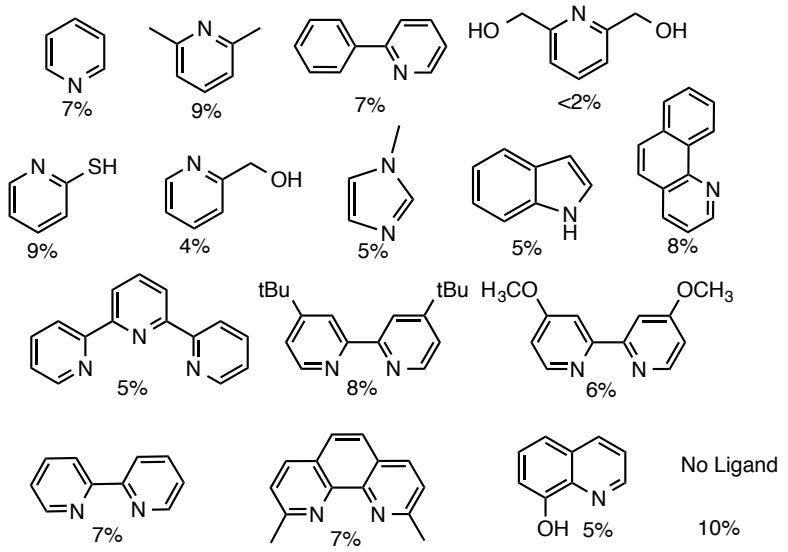
1.2.5. Ligand Screening

Ligands have an electronic effect on copper, which may influence the decarboxylation and oxidation steps. Figure 3 lists all the ligands we tried. Unfortunately, neither monodentate nor polydentate ligands can increase the efficiency of this reaction (Figure 3). The highest yield of **1** is obtained without any additional ligands. This result suggests that the 1,10-phenanthroline itself is the ligand.

Figure 3. Ligand Screening for Trifluoromethylation of Phenanthroline[a]



* Yields[b] below are the yields of product **1**.

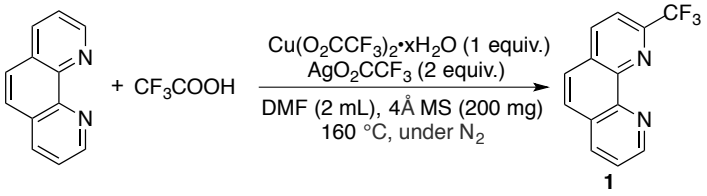


[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), $Cu(O_2CCF_3)_2•xH_2O$ (1 equiv.), AgO_2CCF_3 (2 equiv.), ligands (1 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) in DMF (2 mL) at 160 °C for 24 h under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

1.2.6. Screening of Reaction Time

After trying different reaction times, we found that 10 % yield can be obtained in 6 h (Table 5, entries 1-3). Longer reaction times did not improve the yield of **1** (entries 4-7).

Table 5. Screening of Reaction Time for Trifluoromethylation of Phenanthroline[a]



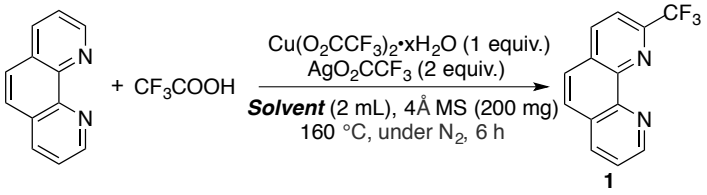
Entry	Reaction Time (h)	Yield (%)[b]
1	2	7
2	4	7
3	**6**	**10**
4	12	10
5	20	10
6	24	10
7	48	10

[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), $Cu(O_2CCF_3)_2•xH_2O$ (1 equiv.), AgO_2CCF_3 (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) at 160 °C in DMF (2 mL) under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

1.2.7. Solvent Screening

Finally, different solvents were explored for this reaction (Table 6). To our disappointment, neither 1,4-dioxane nor xylenes (entries 2 and 3) improved the reaction yield, while dimethylacetamide as the solvent lowered the yield (entry 1).

Table 6. Solvent Screening for Trifluoromethylation of Phenanthroline[a]



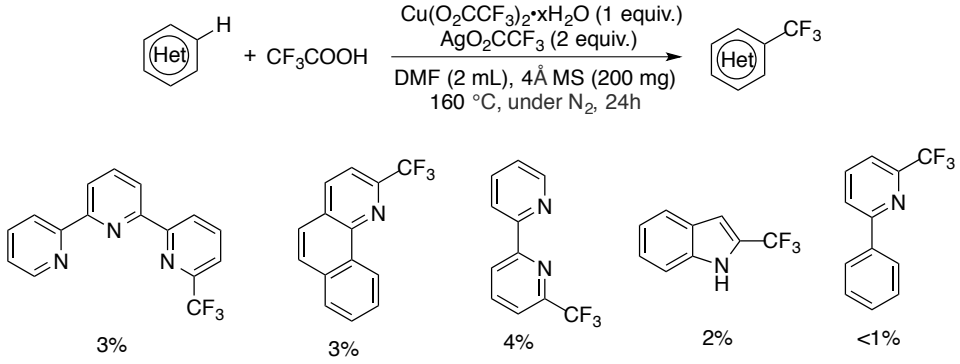
Entry	Solvent	Yield (%)[b]
1	DMA	7
2	1,4-dioxane	NR
3	xylenes	NR
4	**DMF**	**10**

[a]Reaction conditions: 1,10-Phenanthroline (0.2 mmol), $Cu(O_2CCF_3)_2•xH_2O$ (1 equiv.), AgO_2CCF_3 (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) at 160 °C in solvent (2 mL) under N_2 for 6 h in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

1.2.8. Trifluoromethylation of Other Heteroarenes

Other heteroarenes were also tested for their reactivity in this reaction (Figure 4). They can undergo triflruoromethylation, but in low yields.

Figure 4. Heteroarenes Screening for Trifluoromethylation with CF_3CO_2H[a]



[a]Reaction conditions: Heteroarene (0.2 mmol), $Cu(O_2CCF_3)_2•xH_2O$ (1 equiv.), AgO_2CCF_3 (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) at 160 °C in solvent (2 mL) under N_2 for 24 h in a 25 ml Schlenk tube. Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

1.3. Conclusion

We have developed a copper-mediated oxidative decarboxylative C-H trifluoromethylation of 1,10-phenanthroline using TFA as the trifluoromethylating reagent. Control reactions showed the essential role of copper in this reaction. Various oxidants, copper catalysts, ligands, temperatures, reaction time and solvents have been explored. None of these factors can imrpove the reaction yield above 10%.

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Chapter II

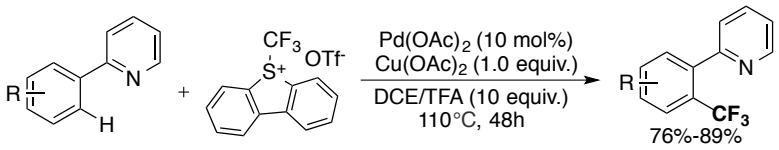
Directed Trifluoromethylation of Arene C-H Bonds Using Trifluoroacetic Acid as the CF_3 Source

2.1. Introduction

2.1.1. Palladium-Catalyzed Trifluoromethylation via a Directing Group

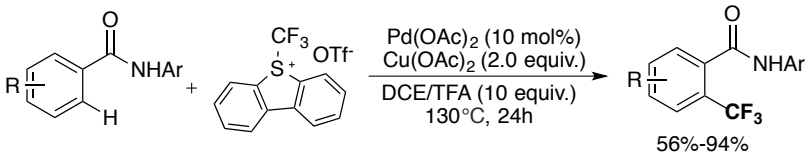
Aryl palladium species can be generated by palladium-catalyzed aryl C-H bond activation.[1] These species have been demonstrated to react with nucleophiles[2] and electrophiles[3] to form the cross-coupling products. Importantly, applying CF_3^- as the nucleophile[4] or CF_3^+ as the electrophile,[5] palladium is able to catalyze the introduction of CF_3 on to arenes.

The selective trifluoromethylation of arenes is very important for the synthesis of pharmaceuticals and agrochemicals. Incorporating CF_3 onto the *ortho* position of arenes bearing a directing group can allow trifluoromethylation of arenes with high selectivity. Palladium-catalyzed amination,[6a] arylation,[6b] and other[6c] reactions via a directing group have been reported in the past few decades. For example, in 2010, Yu's group developed a new Pd(II)-catalyzed *ortho* trifluoromethylation of 2-phenylpyridine through C-H activation using a directing group (Eq 7).[7]



(7)

After two years, their group reported the Pd(II)-catalyzed trifluoromethylation of arenes using amide as the directing group (Eq 8).[8] However, to the best of our knowledge, there are no examples of copper-mediated directed trifluoromethylation reactions using trifluoroacetic acid as the CF_3 source.

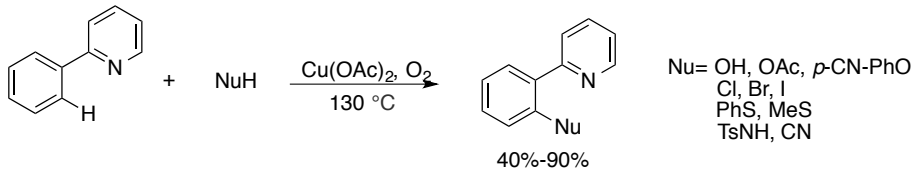


(8)

2.1.2. Copper-Mediated Directed Functionalization

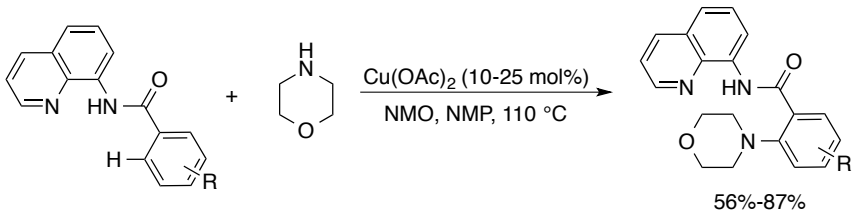
Notably, palladium catalysts have demonstrated extraordinary versatility in the directed C-H functionalization reactions to form carbon-carbon and carbon-heteroatom bonds.[9a, 9b] It is highly desirable to develop analogous reactions using inexpensive metals such as copper.

In 2006, Yu's group reported a diverse range of Cu-catalyzed or Cu-mediated C–H activation/carbon–heteroatom-forming reactions of 2-phenylpyridine with various nucleophiles (Eq 9).[10]



(9)

In 2013, Daugulis's group developed a method for the copper-catalyzed auxiliary-assisted amination of arene C-H bonds (Eq 10).[11] The key to its success is the coordination from the picolinamide directing group.



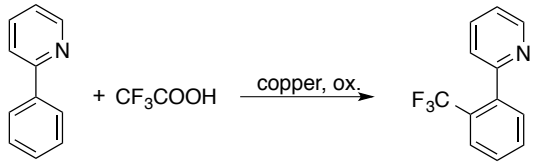
(10)

Based on this work, we can see that copper can mediate the directed functionalization reactions of arene C-H bonds with nucleophiles. However, as far as our knowledge, there are no literature reports of a copper-mediated directed trifluoromethylation.

2.1.3. Project objective

Our target is to develop a copper-mediated or copper-catalyzed *ortho* trifluoromethylation of 2-phenylpyridine using trifluoroacetic acids as the CF_3 source.

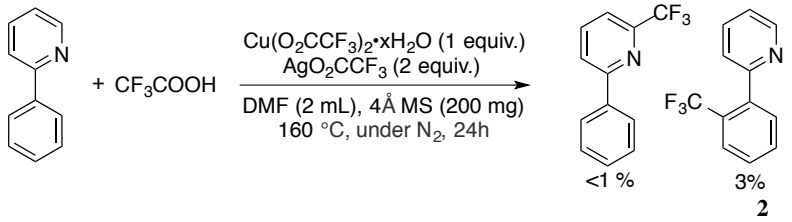
We hypothesized a possible pathway for this reaction, based on the mechanism proposed by Yu and coworkers for the related copper-catalyzed oxidative functionalization of aryl C-H bonds.[10] The reaction begins with decarboxylation of CF_3CO_2H, generating the nucleophilic [$CuCF_3$]. Next, *ortho* C-H activation will form an aryl-copper-trifluoromethyl intermediate. *Ortho* trifluoromethylated 2-phenylpyridine can be generated after reductive elimination (Scheme 10).



Scheme 10. Objective of Copper-Mediated Directed Trifluoromethylation

2.2. Results and Discussion

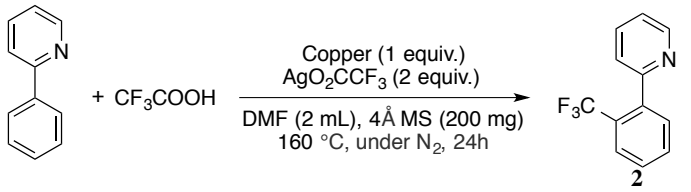
In the trifluoromethylation reaction of 2-phenylpyridine (see Chapter I), the *ortho* trifluoromethylated product (**2**) was also found and characterized based on the literature (Eq 11).[7]



(11)

In order to improve the yield of **2**, various copper salts were tested (Table 7). From the table we can see that CuBr, CuI and $CuCl_2$ (entries 2, 4 and 6) gave approximately the same yield.

Table 7. Copper Screening for Directed Trifluoromethylation[a]

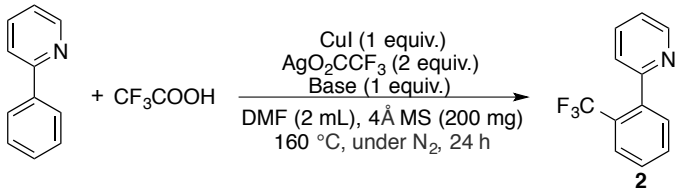


Entry	Copper	Yield (%)[b]
1	CuCl	3
2	**CuBr**	**4**
3	CuOAc	<1
4	**CuI**	**4**
5	Cu_2O	2
6	**$CuCl_2$**	**4**
7	$CuBr_2$	3
8	$Cu(OAc)_2.H_2O$	<1
9	$Cu(CF_3COO)_2•xH_2O$	3

[a]Reaction conditions: 2-Phenylpyridine (0.2 mmol), copper (1 equiv.), AgO_2CCF_3 (2 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) in DMF (2 mL) at 160 °C for 6 h under N_2 in a 25 mL Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

Furthermore, bases were also tested for this reaction (Table 8). Among all the bases explored, Cs_2CO_3, K^{t}OBu and NaOAc (entries 2-4) inhibited the reaction, and KF provided a lower yield (2%, entry 5). Therefore, the reaction without a base provides a better yield.

Table 8. Copper-Mediated Directed Trifluoromethylation of Bases Screening[a]



Entry	Base	Yield (%)[b]
1	**--**	**4**
2	Cs_2CO_3	<1
3	K^{t}OBu	<1
4	NaOAc	<1
5	KF	2

[a]Reaction conditions: 2-Phenylpyridine (0.2 mmol), CuI (1 equiv.), AgO_2CCF_3 (2 equiv.), Base (1 equiv.), CF_3CO_2H (1.5 equiv.), and 4Å MS (200 mg) in DMF (2 mL) at 160 °C for 24 h under N_2 in a 25 ml Schlenk tube. [b]Yields were determined by ^{19}F NMR spectroscopy using 1,3,5-tris(trifluoromethyl)benzene as the internal standard.

2.3. Conclusion

An *ortho* trifluoromethylated 2-phenylpyridine has been obtained with stoichiometric loading of copper salt and CF_3CO_2H as the CF_3 source. Copper salts and bases had been explored. Additional investigation of this reaction is needed to optimize the reaction condition.

2.4. References

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Chapter III

Copper-Catalyzed Decarboxylative C-H Arylation of Benzoxazoles with Benzoic Acids

3.1. Introduction

Many widely used pharmaceuticals and agrochemicals contain biaryl structures as the main components for biological and functional activity.[1] Valsartan and Telmisartan are important medicines for the treatment of high blood pressure, while Boscalid is a fungicide. Each of these molecules contain the biaryl structure as an essential part for their biological activities (Figure 3).[1]

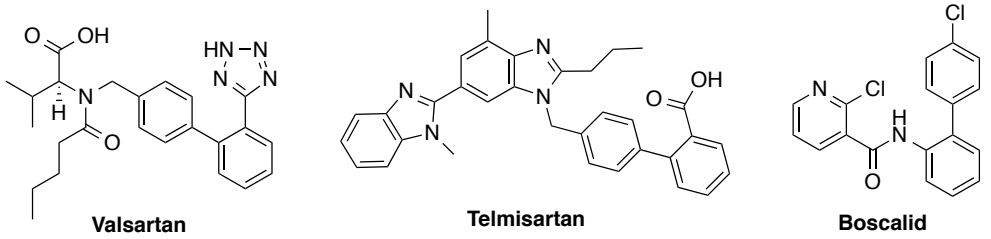


Figure 5. Examples of Pharmaceuticals and Agrochemicals Bearing Biaryl Structures

Over the last few decades, the formation of carbon-carbon bonds to build biaryl structures has evolved into a key synthetic approach for the construction of organic compounds.[2] Various cross-coupling methods have been developed, for example, the Suzuki,[3a] Negishi,[3b] and Kumada[3c] reactions (Figure 4). These reactions are classified as coupling reactions with nucleophiles and electrophiles defined by two leaving groups of opposite polarity. Even though these reactions lead to the formation of new carbon-carbon bonds, they are limited by the need for prefunctionalized substrates. Compared with the prefunctionalized substrates in traditional cross-coupling reactions, carboxylic acid derivatives are easier to handle and commercially available in a broad scope, making them ideal starting materials to build biaryl structures.

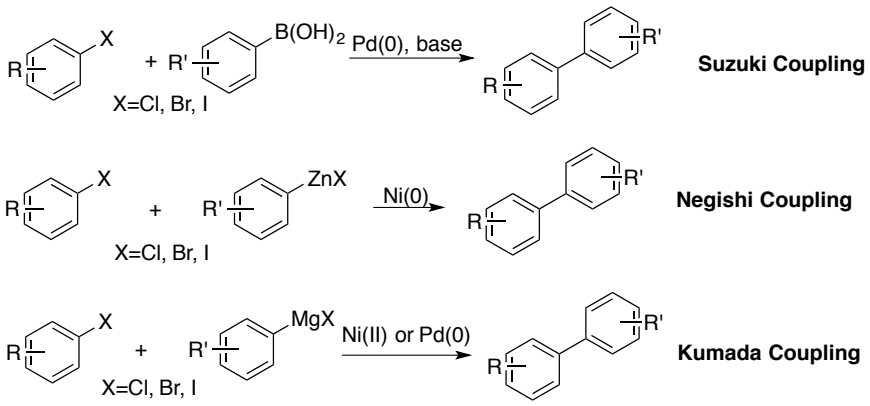
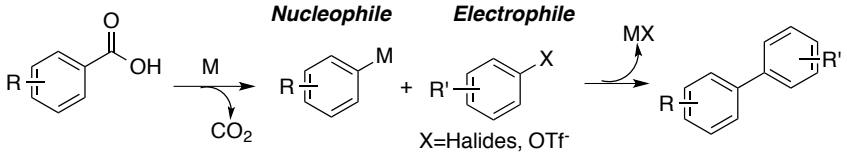


Figure 6. Suzuki, Negishi and Kumada Cross-Coupling Reactions to Build Biaryl Structures

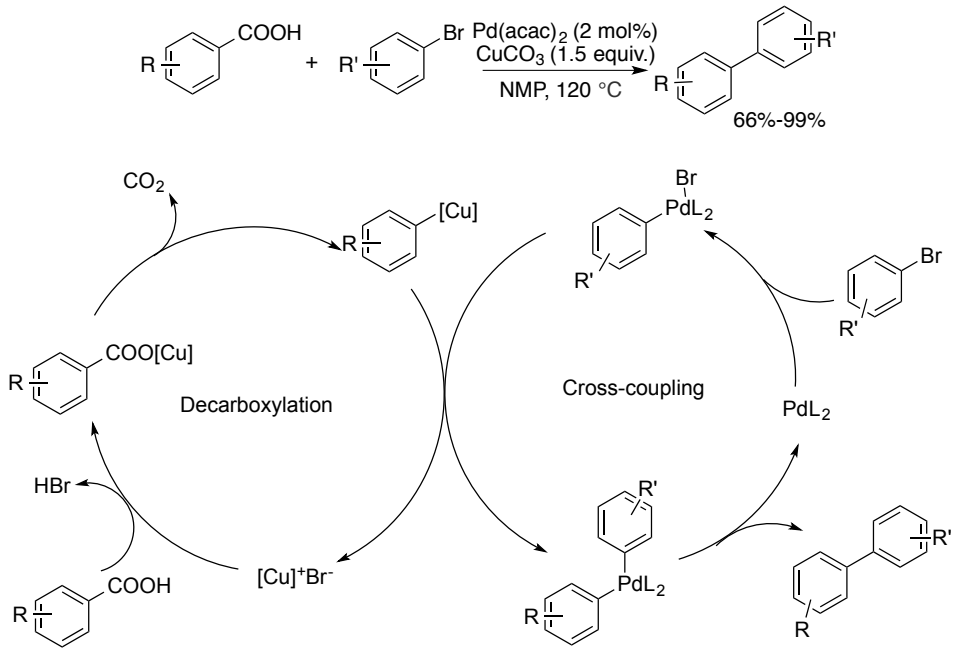
3.1.1. Decarboxylative Coupling of Benzoic Acids with Electrophilic Aryl Groups

Benzoic acids can be converted into carbon nucleophiles by extrusion of CO_2. The resulting nucleophile can be directly coupled with other electrophiles, like aryl halides[1] and aryl triflates,[4] to form the carbon-carbon bonds (Scheme 11).



Scheme 11. Decarboxylative Coupling of Benzoic Acids with Electrophilic Aryl Groups

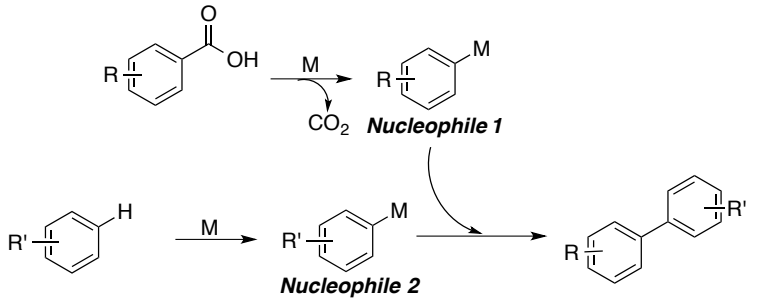
In 2006, Goossen's group reported the decarboxylative coupling of benzoic acids with aryl bromides as the electrophiles.[1] They developed a synthetic method to form the carbon-carbon bond with a bimetallic catalyst system; the copper complex mediates decarboxylation, while a palladium catalyst catalyzes the cross-coupling with an aryl bromide (Scheme 12).



Scheme 12. Decarboxylative Coupling of Benzoic Acids with Aryl Bromides Catalyzed by a Bimetallic Catalyst System

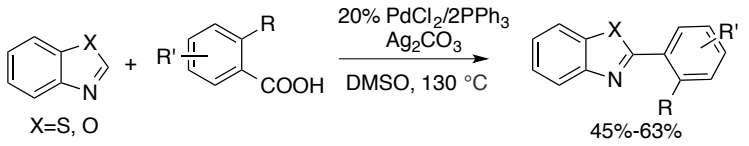
3.1.2. Oxidative Decarboxylative Coupling of Benzoic Acids with Heteroaryl C-H Bonds

Compared with C-X (X=Cl^-, Br^-, and OTf^-) bonds, the more economic and attractive approach to biaryl organic structures with carboxylic acids is the direct arylation of heteroarene C-H bonds. Heteroarenes and benzoic acids can be converted into carbon nucleophiles by C-H bond activation and decarboxylation, respectively. In the presence of an oxidant, the two nucleophiles can be coupled to form the new carbon-carbon bond (Scheme 13).



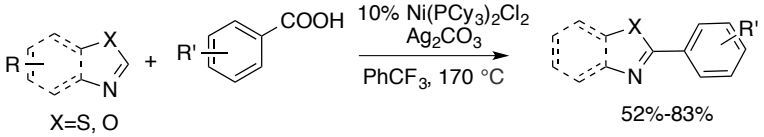
Scheme 13. Oxidative Decarboxylative Coupling of Benzoic Acids with (Hetero)aryl C-H Bonds

In 2010, Tan's group reported a palladium catalyzed oxidative decarboxylative arylation reaction of substituted benzoic acids with heteoarenes, including thiazoles and benzoxazoles (Eq 12).[5]



(12)

In 2014, Zhang and Lu developed a nickel-catalyzed oxidative decarboxylative cross-coupling of azole derivatives, in particular benzoxazoles, with benzoic acids (Eq 13).[6]



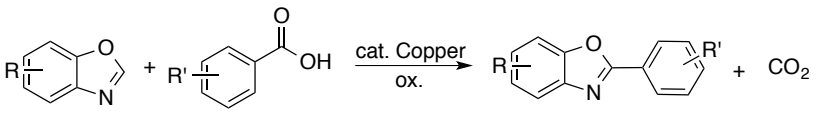
(13)

Copper has been demonstrated to catalyze the decarboxylation of aromatic carboxylic acids.[7] In addition, copper can catalyze the oxidative arylation of acidic (hetero)aryl C-H bonds.[8] Moreover, compared with the transition metals mentioned above, copper is less expensive and can be more easily removed from the final product. It is highly desirable to develop a copper-catalyzed oxidative decarboxylative coupling of benzoic acids with heteroarenes.

3.1.3. Project Objective

Our target is to develop a copper catalyzed oxidative decarboxylative coupling reaction. Based on the proposed mechanism in Tan's palladium catalyzed oxidative decarboxylative arylation reaction,[5] a proposed pathway to accomplish this transformation is shown in Scheme 14. First, the benzoic acid could be decarboxylated to generate a Cu-aryl complex as the intermediate. Then this complex will undergo a C-H activation to form a benzoxazole-Cu-aryl complex. Finally, after reductive elimination,

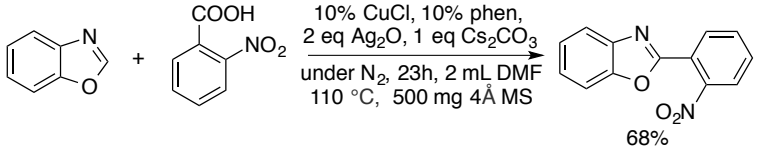
the carbon-carbon bond can be formed with the regeneration of the copper for the next cycle (Scheme 14).



Scheme 14. Proposed Oxidative Decarboxylative Coupling of Benzoic Acids with (hetero)aryl C-H Bonds.

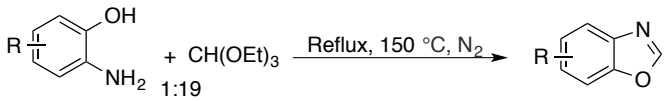
3.2. Results and Discussion

Our group (Lijun Chen) has previously optimized the reaction condition for the copper-catalyzed C-H arylation of benzoxazole and 2-nitrobenzoic acid (Eq 14) and identified the following as the optimal reaction conditions: 0.2 mmol of benzoic acid, 0.3 mmol of benzoxazole, 10% of CuCl, 10% of 1,10-phenanthroline as the ligand, 2 equiv. of Ag_2O as the oxidant, and 1 equiv. of Cs_2CO_3 as the base, in 2 mL DMF at 110 °C under N_2 for 23 h. Under these conditions, the desired coupling product was isolated in 68% yield.



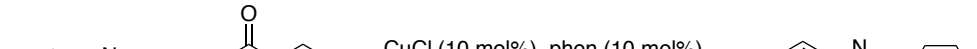
(14)

My work on this project focused on the development of the substrate scope of benzoxazoles as shown in Table 9. Of the benzoxazoles studies, only 5-methyl benzoxazole is commercially available, all other benzoxazoles were synthesized from reaction of the appropriately substituted 2-aminophenol with triethylorthoformate ($CH(OEt)_3$) at 150 °C under N_2 (Eq 15).



(15)

Table 9. Copper-catalyzed Decarboxylative C-H arylation of Substituted Benzoxazoles[a]



entry	product	yield[b]	entry	product	yield[b]
1	**3a** **4a**	68%	6	**3f** **4f**	62%
2	**3b** **4b**	33%	7	**3g** **4g**	47%
3	**3c** **4c**	28%	8	**3h** **4h**	48%
4	**3d** **4d**	37%	9	**3i** **4i**	60%
5	**3e** **4e**	70%			

[a]Reaction conditions: **4** (0.6 mmol), **3** (1.5 equiv.), CuCl (10%), 1,10-phenanthroline (10%), Ag_2O (2 equiv.), Cs_2CO_3 (1equiv.), and 4Å MS (1.5 g) in 6 mL DMF at 110 °C under N_2 for 23 h in a 50 mL Schlenk tube. [b]Isolated yields.

Eight benzoxazoles (**3b**-**3i**) were synthesized according to this method. We tested the reactivity of each under our copper-catalyzed oxidative decarboxylative coupling conditions (Table 9). Benzoxazoles bearing various substituents underwent decarboxylative arylation smoothly to give the corresponding coupling products (**4a-4i**) in moderate yields. Functional groups, such as chloro- and bromo-, were compatible with the catalyst system (**3b**, **3c**, and **3h**). Furthermore, for the 5-substituted benzoxazoles, compared with electron-rich benzoxazoles (**3a**, **3e**, and **3f**), electron-deficient benzoxazoles (**3b**, **3c**, and **3d**) were less reactive in this reaction. In addition, the effect of substituents at different positions of benzoxazoles was also tested. For the methyl substituted benzoxazoles, 5-methyl benzoxazoles (**3a**) was more reactive than 7-methyl benzoxazole (**3g**).

3.3. Conclusion

An efficient method for the copper-catalyzed oxidative decarboxylative C-H arylation of benzoic acids with benzoxazoles has been developed. Using this method, a wide range of benzoic acids and benzoxazoles were converted into their corresponding coupling products in moderate to excellent yields. Importantly, most common functionalities, such as nitro-, chloro- and bromo-substituents, are well-tolerated.

3.4. References

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Experimental Procedures

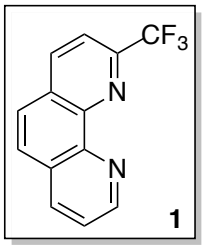
I. General Information

Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates and visualization on TLC was achieved by UV light (254 nm). Flash column chromatography was undertaken on silica gel. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra was recorded at 400 MHz and chemical shifts were reported in parts per million (ppm) referenced to the appropriate solvent peak. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. Coupling constants, *J*, were reported in Hz.

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Benzoxazole, 5-methylbenzoxazole were purchased and used as received. Other benzoxazole derivatives were synthesized by the following procedure in Part IV.

II. Optimization Study – Presentative Procedure for Copper-Mediated Oxidative Decarboxylative Trifluoromethylation of Phenanthroline

1,10-phenanthroline (0.2 mmol, 36 mg), CuCl (0.2 mmol, 20 mg), AgO_2CCF_3 (0.4 mmol, 88 mg), and 4Å MS (200 mg) were combined in a 25 mL Schlenk tube fitted with a septum and a stir bar. The tube was evacuated and backfilled with N_2 three times. Then trifluoroacetic acid (0.3 mmol, 22.5 uL) was added after the addition of DMF (0.15 M, 2 mL). The reaction mixture was stirred under N_2 at room temperature for 5 min, then continued at 160°C for 24 h. Upon completion, the reaction was cooled to room temperature and diluted with ethyl acetate. The mixture was filtered through celite and the solvent was removed under vacuum. 1,3,5-tris(trifluoromethyl)benzene (0.02 mmol, 5.6 mg) was added as an internal standard. The yield was determined by ^{19}F NMR. The crude mixture was purified by silica column chromatography to yield 2-trifluoromethyl-1,10-phenanthroline.

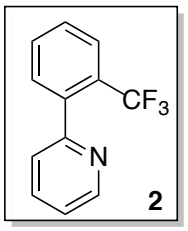


2-trifluoromethyl-1,10-phenanthroline (1)

The crude material was purified by silica column chromatography (R_f = 0.21 in 1:1 Hex:EtOAc) to yield 1.0 mg (2%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.30 (dd, *J*= 8, 1, 1H), 8.45 (d, *J*= 8, 1H), 8.30 (dd, *J*= 8, 1, 1H), 8.0 (d, *J*= 8, 1H), 7.90 (d, *J*= 8, 1H), 7.87 (d, *J*= 8, 1H), 7.70 (dd, *J* = 8, 1, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -66.57.

III. Optimization Study – Presentative Procedure for Copper-Mediated Directed Trifluoromethylation of Arene C-H Bonds

CuCl (0.2 mmol, 20 mg), AgO_2CCF_3 (0.4 mmol, 88 mg), and 4Å MS (200 mg) were combined in a 25 mL Schlenk tube fitted with a septum and a stir bar. The tube was evacuated and backfilled with N_2 three times. Then 2-phenylpyridine (0.2 mmol, 29 uL) and trifluoroacetic acid (0.3 mmol, 22.5 uL) were added after the addition of DMF (0.15M, 2 mL). The reaction mixture was stirred under N_2 at room temperature for 5 min, then continued at 160°C for 24 h. Upon completion, the reaction was cooled to room temperature and diluted with ethyl acetate. The mixture was filtered through celite and the solvent was removed under vacuum. 1,3,5-tris(trifluoromethyl)benzene (0.02 mmol, 5.6 mg) was added as an internal standard. The yield was determined by ^{19}F NMR. The crude mixture was purified by silica column chromatography to yield 2-(2-trifluoromethylphenyl)pyridine.

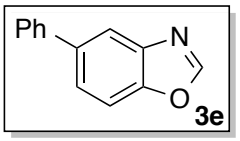


2-(2-trifluoromethylphenyl)pyridine (2)

The crude material was purified by silica column chromatography (R_f = 0.56 in 1:1 Hex:EtOAc) to yield 2.0 mg (3%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (dd, *J*= 8, 1, 1H), 7.75 (m, 2H), 7.60 (m, 1H), 7.53 (m, 2H), 7.42 (d, *J*= 8, 1H), 7.30 (m, 1H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ -56.80.

IV. Presentative Procedure for the Synthesis of Substituted Benzoxazoles

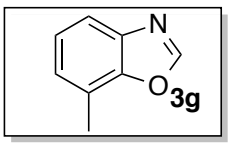
A mixture of 2-amino-5-methoxyphenol (5.7 mmol, 1 g) and triethyl orthoformate (109 mmol, 23 mL) was heated under reflux (at 150 °C). The reaction was allowed to run until no starting 2-aminophenol remained as determined by TLC. Upon completion, after cooling to room temperature, remaining triethyl orthoformate was removed by distillation and the residue was purified by column chromatography (EtOAc/hexane, 1:20).



5-phenylbenzoxazole (3e)

Isolated yield: 85%

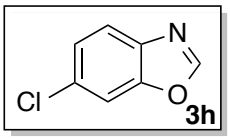
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.98 (m, 1H), 7.60 (m, 4H), 7.44 (m, 2H), 7.38 (m, 1H).



7-methylbenzoxazole (3g)

Isolated yield: 55%

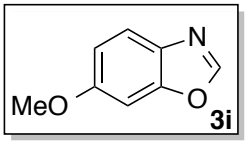
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (s, 1H), 7.60 (d, *J* = 8, 1H), 7.24 (t, *J* = 8, 1H), 7.16 (d, *J* = 8, 1H), 2.48 (s, 3H).



6-chlorobenzoxazole (3h)

Isolated yield: 62%

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.69 (d, *J* = 8, 1H), 7.60 (d, *J* = 2, 1H), 7.35 (dd, *J* = 8, 2, 1H).



6-methoxybenzoxazole (3i)

Isolated yield: 64%

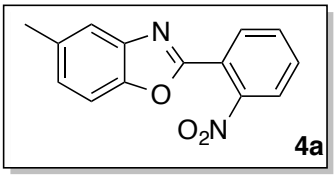
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H), 7.63 (d, *J* = 8, 1H), 7.08 (d, *J* = 2, 1H), 6.95 (dd, *J* = 8, 2, 1H), 3.86 (s, 3H).

V. Presentative Procedure for the Direct Arylation of Substituted Benzoxazoles with 2-Nitrobenzoic Acid.

For the reactions of 0.6 mmol scale of 2-nitrobenzoic acid:

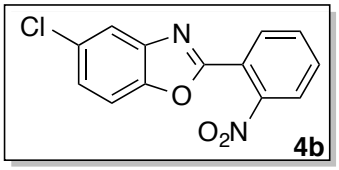
2-Nitrobenzoic acid (0.6 mmol, 108 mg), CuCl (0.06 mmol, 6 mg), phen (0.06 mmol, 11 mg), Cs_2CO_3 (0.6 mmol, 195 mg), Ag_2O (1.2 mmol, 279 mg), and 4Å MS (1.5 g) were combined in a 50 mL Schlenk tube fitted with a septum and a stir bar. The tube was evacuated and backfilled with N_2 three times before a solution of 6-chlorobenzoxazole (0.9 mmol, 138 mg) in DMF (0.3 M, 6 mL) was added. The reaction mixture was stirred under N_2 at 110°C for 23 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered through celite and the solvent was removed under vacuum. The crude mixture was purified by silica column chromatography to yield the title compound.

VI. Characterization of Oxidative Decarboxylative Cross-Coupling Products.



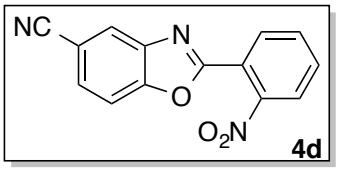
5-methyl-2-(2-nitrophenyl)-benzo[d]oxazole (4a)

The crude material was purified by silica column chromatography (R_f = 0.56 in 1:1 Hex:EtOAc) to yield 103.4 mg (0.41 mmol, 68% y) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (dd, *J*= 8, 1, 1H), 7.85 (dd, *J*= 8, 1, 1H), 7.67 (m, 2H), 7.57 (d, *J*= 1, 1H), 7.41 (d, *J*= 8, 1H), 7.18 (dt, *J*= 8, 1, 1H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.78, 149.28, 141.72, 134.84, 132.26, 131.67, 131.32, 127.16, 125.66, 124.12, 121.58, 120.48, 110.26, 21.47.



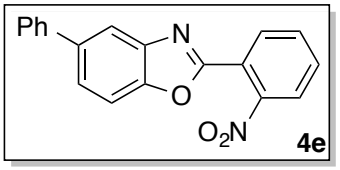
5-chloro-2-(2-nitrophenyl)-benzo[d]oxazole (4b)

The crude material was purified by silica column chromatography (R_f = 0.33 in 1:1 Hex:EtOAc) to yield 54.3 mg (0.19 mmol, 33% y) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (dd, *J* = 8, 2, 1H), 7.89 (dd, *J* = 8, 2, 1H), 7.78 (d, *J* = 8, 1H), 7.71 (m, 3H), 7.47 (d, *J* = 8, 1H), 7.37 (dd, *J* = 8, 2, 1H).



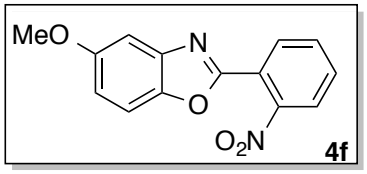
5-cyano-2-(2-nitrophenyl)-benzo[d]oxazole (4d)

The crude material was purified by silica column chromatography (R_f = 0.36 in 1:1 Hex:EtOAc) to yield 58.3 mg (0.22 mmol, 37% y) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (m, 2H), 7.96 (dd, *J* = 8, 2, 1H), 7.77 (m, 4H).



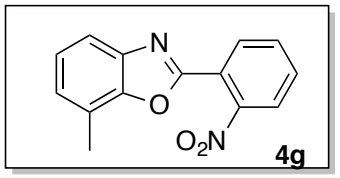
5-phenyl-2-(2-nitrophenyl)-benzo[d]oxazole (4e)

The crude material was purified by silica column chromatography (R_f = 0.31 in 1:1 Hex:EtOAc) to yield 132.9 mg (0.42 mmol, 70% y) of the title compound as a light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (dd, *J* = 8, 2, 1H), 7.99 (dd, *J* = 8, 2, 1H), 7.89 (dd, *J* = 8, 2, 1H), 7.69 (m, 2H), 7.61 (m, 4H), 7.46 (m, 2H), 7.36 (m, 1H).



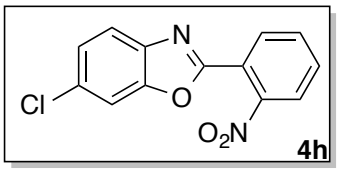
5-methoxy-2-(2-nitrophenyl)-benzo[d]oxazole (4f)

The crude material was purified by silica column chromatography (R_f = 0.50 in 1:1 Hex:EtOAc) to yield 100.4 mg (0.37 mmol, 62% y) of the title compound as a white solid. ^{1}H NMR (Acetone-d_6, 400 MHz): δ 8.19 (dd, *J* = 8, 2, 1H), 8.01 (dd, *J* = 8, 2, 1H), 7.86 (m, 2H), 7.55 (d, *J* = 8, 1H), 7.27 (d, *J* = 8, 1H), 7.02 (dd, *J* = 8, 2, 1H), 3.87 (s, 3H).



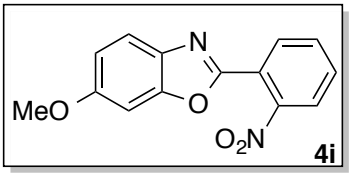
7-methyl-2-(2-nitrophenyl)-benzo[d]oxazole (4g)

The crude material was purified by silica column chromatography (R_f = 0.53 in 1:1 Hex:EtOAc) to yield 109.3 mg (0.28 mmol, 47% y) of the title compound as a white solid ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (dd, *J* = 8, 1, 1H), 7.86 (dd, *J* = 8, 1, 1H), 7.64 (m, 3H), 7.26 (dt, *J* = 8, 1, 1H), 7.15 (d, *J* = 2, 1H), 2.50 (s, 3H).



6-chloro-2-(2-nitrophenyl)-benzo[d]oxazole (4h)

The crude material was purified by silica column chromatography (R_f = 0.29 in 1:1 Hex:EtOAc) to yield 139.6 mg (0.29 mmol, 48% y) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.13 (dd, *J* = 8, 2, 1H), 8.11 (dd, *J* = 8, 2, 1H), 7.96 (d, *J* = 8, 1H), 7.88 (dd, *J* = 8, 2, 2H), 7.83 (d, 1H), 7.44 (dd, *J* = 8, 2, 1H).



5-methyl-2-(2-nitrophenyl)-benzo[d]oxazole (4i)

The crude material was purified by silica column chromatography (R_f = 0.59 in 1:1 Hex:EtOAc) to yield 96.8 mg (0.36 mmol, 60% y) of the title compound as a white solid ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (dd, *J* = 8, 1, 1H), 7.82 (dd, *J* = 8, 1, 1H), 7.70 (m, 3H), 7.06 (d, *J* = 2, 1H), 6.97 (dd, *J* = 8, 2, 1H), 3.85 (s, 3H).